REMARKS

The Office Action stated that claims 1-23 are pending. Actually, claims 21-23 were cancelled in the Response dated July 19, 2004 (Response, page 2, Listing of the Claims). Thus, claims 1-20 are pending. However, Applicants inadvertently omitted stating that claims 21-23 are cancelled in the "Remarks" section of the Response dated July 19, 2004. If, for that omission claims 21-23 were not cancelled, Applicants hereby cancel claims 21-23 without prejudice as to their subject matter.

Claims 1-6 and 11-20 have been cancelled without prejudice. Claim 7 has been amended and claim 24 is newly presented. Support for the amendment of claim 7 can be found throughout the specification and specifically at page 19, lines 5 and 6. Support for new claim 24 can be found at page 14, lines 1-10. No new matter is introduced with these amendments. With the entering of this amendment claims 7-10 and 24 will be pending.

Applicants would like to thank the Examiner for his courtesies at the interview on February 23, 2005.

I. The Claims of the Instant Invention are Patentable over Japanese Patent Application H5-194225

Claims 1-23 stand rejected under 35 U.S.C. § 103(a) as unpatentable over H5-194225 ("Oishi").

Oishi teaches the preparation of tablets having benzimidazole ATPase inhibitors stabilized with amino acids and buffering agents when employed simultaneously. To demonstrate the stability of the benzimidazole ATPase inhibitors with amino acids and buffering agents, Oishi dispersed omeprazole ("OM") in 20 ml of water along with either glycine, alanine, threonine, isoleucine, or phenylalanine, and $Na_2HPO_4 \cdot 12H_2O$ as the buffering agent. Oishi then observed "the change in the external appearance over time of the white suspension" and disclosed the results (Oishi, Example of Embodiment 1, Table 1).

Oishi discloses that the stabilizing agents "are in the ranges of 0.01-10 parts by weight of amino acid and 0.01-10 parts by weight of buffering agent per 1 part by weight of benzimidazole compound." (Oishi page 5, lines 1-2). These ranges represent a molecular ratio of amino acid ("aa") to benzimidazole ("BI") (aa:BI) of 0.046:1 to 4.5:1 (selecting glycine as the amino acid). These ratios are determined by calculating the molecular amounts of glycine (MW 75 $gmol^{-1}$) and omeprazole (MW 348 $gmol^{-1}$). Thus, the molecular ratio of 0.01 g glycine:1 g omeprazole is calculated:

0.01 g glycine * 1 mole/75 g = $1.33*10^{-4}$ moles glycine;

1 g omeprazole * 1 mole/348 g = $2.9*10^{-3}$ moles omeprazole;

$1.33*10^{-4}$ moles glycine: $2.9*10^{-3}$ moles omeprazole = 0.046:1 gly:OM.

The molecular ratio of 10 g glycine:1 g omeprazole is calculated:

10 g glycine * 1 mole/75 g = $1.33*10^{-1}$ moles glycine;

1 g omeprazole * 1 mole/348 g = $2.9*10^{-3}$ moles omeprazole;

$1.33*10^{-1}$ moles glycine: $2.9*10^{-3}$ moles omeprazole = 4.6:1 gly:OM.

Therefore the broadest molecular ratio disclosed is 0.046:1 to 4.6:1 gly:OM.

Oishi discloses one example having 100 mg glycine and 100 mg omeprazole as a suspension (not a solution) which represents a molecular ratio of glycine:omeprazole of 4.58:1 (gly:OM) (calculated as outlined above) (Oishi page 6, Example of Embodiment 1). Oishi also discloses a solid tablet having 2.5 mg glycine and 5.0 mg omeprazole. This represents a molecular ratio of glycine:omeprazole of 2.29:1 (gly:OM) (Oishi, page 7, lines 7-8).

The Applicants' claimed intravenous aqueous pharmaceutical formulation is directed to the species rabeprazole. The claims have been amended to recite a ratio of glycine to rabeprazole of between 0.43:1 and 1:1 (based on Applicants disclosure of glycine at 5 mM and 10 mM and rabeprazole at 4 mg/ml which is 11.5 mM (calculated as follows: 0.004 g/1 ml (RB)

* 1 mole/362 g (RB) * 1000 ml/1 L = 11.5 mM) (at page 19, lines 5 and 6). Applicants have found that a very small molecular ratio of glycine to rabeprazole will prevent the discoloration of an intravenous aqueous solution of rabeprazole. The applicants have also amended the body of the claim to recite "wherein the formulation is suitable for intravenous administration." Applicants believes that these amendments distinguish the presently claimed invention over Oishi.

Oishi's singular example of a benzimidazole compound in liquid form is omeprazole dispersed in a suspension. A dispersion and a suspension are not the same as a solution. The term "solution" is defined as "(a) the act or process by which a solid ... is uniformly mixed with ... [a] liquid; (b) the homogeneous mixture formed by this process; (c) the condition of being dissolved" (Hammond Barnhart Dictionary of Science, 1st ed. 1986, p. 607). The term "dissolve" is defined as "to cause to pass into solution; turn into a solute" (*Id.* at page 170). The term "suspension" is defined as "a mixture in which very small particles of a solid remain suspended without dissolving" (*Id.* at p. 643). Thus, a suspension by definition is not a solution. Therefore, Oishi does not disclose an aqueous solution of rabeprazole nor a solution suitable for intravenous administration.

Oishi discloses a very broad range for ratios of amino acids to benzimidazoles in general, *supra*. Applicants recited limitation falls within this range. However, the MPEP states "if the reference's disclosed range is so broad as to encompass a very large number of possible distinct compositions, this might present a situation analogous to the obviousness of a species when the prior art broadly discloses a genus (In re Peterson, 315 F.3d 1325)" (MPEP, 2144.05(I)). Indeed Oishi's broad range encompasses a very large number of distinct compositions given Oishi's disclosure that amino acids when used with a buffering agent will stabilize benzimidazole compounds in tablet form. Oishi discloses no examples of glycine with rabeprazole. Oishi does disclose two examples of glycine with the benzimidazole omeprazole at a ratio of glycine:OM of 4.58:1 and 2.29:1, *supra*. Contrasting the broad range of ratios of amino acids to benzimidazoles disclosed by Oishi with the two examples of ratios of glycine to omeprazole, it is submitted that it would not have been obvious to one of ordinary skill in the art at the time of the invention to choose the range of molecular ratio of between 0.43:1 and 1.0:1.0 of glycine:rabeprazole as

claimed in the instant invention. Thus, Applicants claimed invention is not obvious in view of the disclosure of Oishi. Therefore, Applicants respectfully request that the obviousness rejection based on Oishi be withdrawn.

II. The Claims of the Instant Invention are Patentable over U.S. 5,536,735

Claims 1-23 stand rejected under 35 U.S.C. § 103(a) as unpatentable over U.S. 5,536,735 (" '735" patent) ("Takechi").

Takechi teaches a pharmaceutical composition having a benzimidazole compound having anti-ulcer activity stabilized with a water-soluble carboxylic acid amide (col. 1, line 55). The composition can contain various additives such as surfactants (col. 9, line 15), preservatives (col. 9, line 65), pH control agents (col. 10, line 10), and a variety of salts (col. 9, line 52). This composition can be in the form of an aqueous solution (col. 8, line 6) and preferably a lyophilizate (col. 9, line 65).

Takechi discloses that "these additives can be used alone or in combination and can be added in a proportion of about 0.001-10 mg, preferably 0.01-5 mg, per 1 mg of the benzimidazole compound." (col. 10, lines 12-15). The broadest range represents a molecular ratio of additive to benzimidazole of 0.0049:1 to 49:1 (using an amino acid as the additive and selecting glycine as the amino acid). The preferable range represents a molecular ratio of 0.049:1 to 24.5:1 of additive:benzimidazole. Takechi discloses one example having 375 mg glycine and 1000 mg lansaprazole ("LP") which represents a molecular ratio of glycine to lansaprazole of 1.86:1 (glycine:LP) (Col. 11, line 66ff). These ratios are determined by calculating the molecular amounts of glycine (MW 75 $gmol^{-1}$) and lansaprazole (MW 372 $gmol^{-1}$). Thus, the molecular ratio of 0.001 mg glycine:1 mg lansaprazole is calculated:

0.001 mg glycine * 1 mole/75 g * 1 g/1000 mg = $1.33*10^{-8}$ moles glycine;

1 mg lansaprazole ("LP")* 1 mole/372 g *1 g/1000 mg = $2.7*10^{-6}$ moles LP;

$1.33*10^{-8}$ moles glycine: $2.7*10^{-6}$ moles LP = 0.0049:1 gly:LP.

The molecular ratio of 10 mg glycine:1 mg LP is calculated:

10 mg glycine * 1 mole/75 g * 1g/ 1000 mg = $1.33*10^{-4}$ moles glycine;

1 mg LP * 1 mole/348 g * 1 g/1000 mg = $2.7*10^{-6}$ moles LP;

$1.33*10^{-4}$ moles glycine: $2.7*10^{-9}$ moles LP = 49:1 gly:LP.

Therefore the broadest molecular ratio disclosed is 0.0049:1 to 49:1 gly:LP.

Takechi's preferred range of additive:lansaprazole is 0.01 mg to 5 mg glycine to 1 mg lansaprazole. If glycine is chosen the molecular ratio of the preferred range is calculated as follows:

the molecular ratio of 0.01 mg glycine:1 mg lansaprazole is calculated:

0.01 mg glycine * 1 mole/75 g * 1 g/1000 mg = $1.33*10^{-7}$ moles glycine;

1 mg lansaprazole ("LP")* 1 mole/372 g *1 g/1000 mg = $2.69*10^{-6}$ moles LP;

$1.33*10^{-7}$ moles glycine: $2.7*10^{-6}$ moles LP = 0.049:1 gly:LP.

The molecular ratio of 5 mg glycine:1 mg LP is calculated:

5 mg glycine * 1 mole/75 g * 1g/ 1000 mg = $6.67*10^{-5}$ moles glycine;

1 mg LP * 1 mole/348 g * 1 g/1000 mg = $2.69*10^{-6}$ moles LP;

$6.67*10^{-8}$ moles glycine: $2.69*10^{-9}$ moles LP = 23:1 gly:LP.

Therefore the preferred molecular ratio disclosed is 0.049:1 to 24.8:1 gly:LP.

Takechi's sole example of glycine and lansaprazole is 375 mg glycine to 1000 mg lansaprazole. This molecular ratio is calculated as follows:

375 mg glycine * 1 mol/75 g * 1 g/1000mg = $5.0*10^{-3}$ moles glycine;

1000 mg LP * 1 mol/372 g * 1 g/1000 mg = $2.688*10^{-3}$ moles LP;

$5.0*10^{-3}$ moles glycine to $2.688*10^{-3}$ moles LP = 1.86:1 gly:LP

The Applicants claimed intravenous aqueous pharmaceutical formulation is directed to the species rabeprazole. The claims have been amended to recite a ratio of glycine to rabeprazole of between 0.43:1 and 1:1. Applicants have found that a very molecular ratio of glycine:rabeprazole will prevent the discoloration of an intravenous aqueous solution of rabeprazole. Applicants believe that this amendment distinguishes the presently claimed invention over Takechi.

Takechi's singular example of a benzimidazole compound is lansaprazole, *supra*. Takechi discloses a very broad range for ratios of additives to benzimidazoles in general. Applicants recited limitation falls within that range. However, the MPEP states "if the reference's disclosed range is so broad as to encompass a very large number of possible distinct compositions, this might present a situation analogous to the obviousness of a species when the prior art broadly discloses a genus (In re Peterson, 315 F.3d 1325)" (MPEP, 2144.05(I)). Indeed, Takechi's broad range encompasses a very large number of distinct compositions of a benzimidazole compound stabilized by a water-soluble carboxylic acid amide especially given the disclosure that a variety of widely varying "additives" can be used in these compositions. Takechi discloses no examples of glycine with rabeprazole. Takechi does disclose an example of glycine with the benzimidazole lansaprazole at a ratio of glycine:LP of 2:1, *supra*. Contrasting the broad range of ratios of possible additives to benzimidazoles disclosed by Takechi with the singular example of glycine to lansaprazole, it is submitted that it would not have been obvious to one of ordinary skill in the art at the time of the invention to choose the range of ratios of between 0.43:1 to 1.0:1.0 of glycine:rabeprazole as claimed in the instant invention. Thus, Applicants claimed invention is not obvious in view of the disclosure of Takechi. Therefore, Applicants respectfully request that the obviousness rejection based on Takechi be withdrawn.

CONCLUSION

Applicants respectfully submit that all the bases for rejection of the pending claims are now moot. The Examiner is requested to reconsider the rejections and to withdraw them and to pass this case to issuance.

Respectfully submitted,

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